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Early provision of intrauterine contraception as part of abortion care – 5-year results of a randomised controlled trial

Running title: Early provision of IUD as part of abortion care

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Abstract

Study question: Can the incidence of subsequent termination of pregnancy (TOP) be diminished by providing intrauterine contraception as part of abortion services?

Summary answer: Provision of IUD as part of TOP services reduced the need for subsequent TOP during 5-year follow-up, butand the effect was limited to the first three years.

What is known already: IUD is highly effective in preventing subsequent TOP. Prompt initiation of IUD leads to higher usage rate during follow-up, as compliance with post-TOP IUD insertion visits is low.

Study design, size, duration: The objective of this randomised controlled trial was to assess the effect of early comprehensive provision of intrauterine contraception after TOP on the incidence of subsequent TOP during five years of follow-up.

This study was conducted at Helsinki University Hospital between October 18th 2010 and January 21st 2013. Altogether 748 women undergoing a first trimester TOP were recruited and randomised into two groups. The intervention group (n=375) was provided with an IUD during surgical TOP or 1–4 weeks following medical TOP at the hospital providing the abortion care. Women in the control group (n=373) were advised to contact primary health care for follow-up and IUD insertion. Subsequent TOPs during the 5-year follow-up were identified from the Finnish Register on induced abortions.

Participants, setting, methods: The inclusion criteria were age ≥ 18 years, duration of gestation ≤12 weeks, residence in Helsinki and accepting intrauterine contraception. Women with contraindications to IUD were excluded.

Main results and the role of chance: The overall numbers of subsequent TOPs were 50 in the intervention and 72 in the control group (26.7 vs. 38.6/1000 years of follow-up, p=0.027) and

those of requested TOPs including TOPS and early pregnancy failures 58 and 76 (30.9 vs. 40.8/1000, p=0.080). Altogether 40 (10.7%) women in the intervention and 63 (16.9%) in the control group underwent one or several subsequent TOPs (HR 1.67 [CI 95% 1.13 to 2.49], p=0.011). The number of TOPs was reduced by the intervention during years 0–3 (22.2 vs. 46.5/1000, p=0.035), but not during years 4–5 (33.3 vs. 26.8/1000, p=0.631).

Limitations, reasons for caution: Both medical and surgical TOP were used. This may be seen as a limitation, but it also reflects the contemporary praxis of abortion care. The immediate post-TOP care were provided by two different organizations allowing us to compare two different ways of contraceptive service provision following TOP.

Wider implications of the findings: Providing TOP and IUD insertion comprehensively in a same heath care unit leads to significantly higher rates of attendance, IUD use and significantly lower risk of subsequent TOP (HR 1.67 [CI 95% 1.13 to 2.49], *p*=0.011).

Study funding/competing interest(s): This study was supported by Helsinki University Central Hospital Research funds and by research grants provided by the Jenny and Antti Wihuri Foundation, the Yrjö Jahnsson Foundation, and Finska Läkaresällskapet. EP has received a personal research grant from the Finnish Medical Society. The City of Helsinki supported the study by providing the IUDs. The funding organisations had no role in planning or execution of the study, or in analysing the study results.

Trial registration number: The trial was registered at clinicaltrials.gov (NCT01223521).

Trial registration date: 18th October 2010.

Date of first patient's enrolment: 18th October 2010.

Keywords: Abortion/termination of pregnancy, IUD/intrauterine contraception, subsequent TOP

Ethics approval

We received approvals from the Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS 260/13/03/03/2009), the Ethics Committee of the City of Helsinki (10-1138/054). Approval to carry out the study was granted by the Hospital District of Helsinki and Uusimaa (§12/30.03.2010). The Finnish Institute for Health and Welfare (THL) granted an approval to use personal-level data, which is required for registry-based studies in Finland (THL/1479/5.05.00/2013). All personal-level data that could be used to identify individuals was removed before the analyses.

Transparency statement

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and public information statement

The study was initiated in 2009, and at the time it was not customary to involve patients and/or public in planning of a scientific study.

Dissemination declaration

The study results will be disseminated to the health care providers and organizations involved in the study as well as to the public once the study has been published.

Introduction

The efficacy of long-acting reversible contraceptives (LARCs) and, especially, that of intrauterine devices (IUD) in preventing unwanted pregnancy is well established (Peipert *et al*., 2012; Winner *et al*., 2012; Blumenthal *et al*., 2011; Secura *et al*., 2014). According to several recent guidelines, LARCs have become the recommended method of contraception for women in all age groups (WHO, 2015; RCOG, 2018).

Previous cohort studies have shown that young age, parity, and history of termination of pregnancy (TOP) are associated with increased risk of subsequent TOP (Heikinheimo *et al*., 2008). In addition, contraceptive choices affect the risk of subsequent unwanted pregnancy. In cohort studies, post-abortal use of IUD has been associated with a 60–70% reduction in the need of subsequent TOP (Okusanya *et al*., 2014; Rose *et al*., 2012).

Regardless of the method of TOP, the resumption of ovarian function occurs rapidly; 80% of women ovulate within 6 weeks after TOP (Schreiber *et al*., 2011). In addition, 50% of women resume sexual activity in two weeks following TOP (Boesen *et al*., 2004). Thus, in order to prevent subsequent unwanted pregnancy, immediate initiation of effective contraception is important. In Finland, contraceptive counselling and planning are routinely included in the TOP process, and women are advised to initiate contraceptive use immediately. Yet, more than one in three women undergoing a TOP have a history of one or several previous TOPs. Similar to several other countries, this rate has been increasing during the past decade in Finland (THL, 2018; Socialstyrelsen, 2018; INED, 2012; GOV.UK, 2018).

The insertion of IUD at the time of surgical TOP is effective and safe, and results in higher IUD use during follow-up (Okusanya *et al*., 2014; WHO, 2012; Sääv *et al*., 2012; Bednarek *et al*., 2011).

However, medical abortion has become the dominant method in several countries during the last decades (THL, 2018; Socialstyrelsen, 2018; INED, 2012; GOV.UK, 2018). Medical abortion poses challenges concerning IUD provision since compliance with post-abortion care in the service-delivery systems assessed is often poor (Betstadt *et al*., 2011; Pohjoranta *et al*., 2018). Immediate insertion of an IUD after medical TOP (MTOP) is safe, although it is associated with a higher risk of partial expulsion (Korjamo *et al*., 2017). In contrast, IUD provision at approximately one week after MTOP does not significantly increase the risk of expulsion (Sääv *et al*., 2012; Shimoni *et al*., 2011; Betstadt *et al*., 2011). As with surgical abortion, the prompt provision of IUD leads to a higher rate of use and subject satisfaction following MTOP (Sääv *et al*., 2012).

In the present study, we studied the efficacy of routine provision of IUD as part of abortion care in comparison to the current praxis of prescribing oral contraceptives as a bridging method and directing women to primary health care (PHC) for IUD insertion. Our primary outcome measure was the number of subsequent TOPs performed during the 5-year follow-up after the index abortion. The secondary outcomes were the number of all requested TOPs during the follow-up (including cases of miscarriage, blighted ovum or ectopic pregnancy) and the timing of subsequent TOP. Previously, we published the 1-year follow-up results concerning the need for subsequent TOP, success of early IUD insertion, rates of attendance and IUD use, as well as mental and sexual well-being (Pohjoranta *et al*., 2015; Pohjoranta *et al*., 2017; Pohjoranta *et al*., 2018; Toffol *et al*., 2016). In the present study, we report the final 5-year results on the need for subsequent TOP.

Methods

Study design and participants

This study design has been described in detail previously (Pohjoranta *et al*., 2015). The study was conducted in collaboration with the Helsinki University Hospital and the City of Helsinki.

The inclusion criteria were age ≥18 years, residence in Helsinki, duration of gestation ≤12^{+0} weeks, having a non-foetal indication for the abortion and signing an informed consent form. Women with uterine anomaly, cervical screening result requiring surgical intervention, or inadequate language skills in Finnish or Swedish were excluded. Acute liver disease and breast cancer were contraindications for the levonorgestrel-releasing intrauterine system (LNG-IUS), and copper allergy, iron deficiency anaemia, and Wilson's disease for copper intrauterine device (Cu-IUD). The characteristics of the study participants are presented in Table 1.

Altogether 751 women were randomised into two groups (Figure 1). Women in the intervention group (n=375) were provided with an IUD (either the 52mg levonorgestrel-releasing intrauterine system, LNG-IUS, Mirena® or a Cu-IUD, Nova-T®, both manufactured by Bayer Ag [Turku, Finland] and hereafter referred as IUD) at the hospital responsible for the abortion care. The IUD was planned to be inserted at the time of surgical abortion (n=70), or at a follow-up visit performed 1–4 weeks after MTOP (n=305). Women in the control group (n=373 [71 cases of surgical and 302 medical abortion]) were prescribed oral contraceptives and advised to contact their PHC unit for follow-up and contraceptive services including IUD insertion, according to the current national guideline on induced abortion (Duodecim, 2013). The subsequent TOPs were analysed on an intention-to-treat analysis (ITT) to assess the efficacy of the intended intervention.

Procedures

All abortions were performed according to the national guideline (Duodecim, 2013). All the index abortions in this study were performed due to a social indication, or based on the woman's age of at least 40 years or having given birth to four or more children, both indications for abortion given in the Finnish legislation. The participants were advised to contact the hospital in case of suspected abortion-related adverse events or complications.

According to local guideline of the time, all women were invited for a follow-up at three months after IUD insertion. For the intervention group, this was performed by study nurse. All women were provided a follow-up visit by a specialist in obstetrics and gynaecology (SS) at one and five years at the PHC family planning clinic of the City of Helsinki.

Data on subsequent induced abortions during five years after the index abortion were obtained from the Finnish Register of Induced Abortions kept by the Finnish Institute for Health and Welfare (THL). In Finland, reporting all TOPs to THL is mandatory by the law, and thus the coverage of the register is very high (Heino *et al*., 2018). These data were complemented with data from the electronic patient files of the Hospital District of Helsinki and Uusimaa, where also the requested TOPs later diagnosed as ectopic pregnancies or miscarriages were identified. All cases were reviewed by two members of the study team. In case of a disagreement, a third review was performed. IUD insertion and usage in the control group was followed up to one year using the electronic patient files of the PHC of the City of Helsinki.

Outcomes

The primary outcome of the study was the number of subsequent TOP during five years of follow-up. As a secondary outcome, we analysed all requested TOPs, including cases of miscarriage, ectopic pregnancy or blighted ovum, diagnosed at the time of assessment for TOP.

Randomisation and masking

Randomisation was performed by using computer-assisted permuted-block method with random block sizes of four to six. The investigators did not participate in randomisation, which was done before commencing the study. The group assignments were kept in sealed envelopes, which the study nurse opened after informing and recruiting the women.

Statistical analysis

Based on previous studies, a 15% incidence for subsequent abortion during five years was assumed (Heikinheimo *et al*., 2008). The power calculation was performed with an assumption that the intervention would cause a 50% decrease in the incidence of subsequent abortion. By using the log-rank test, for a power of 80% and a 5% significance level, a total of 350 participants were needed for each group. To cover for the possible loss-to follow-up, 751 women were randomised, and finally 748 women were included in the study. (Figure 1)

The outcomes were calculated by one thousand follow-up years. The Cox proportional hazards model was used for calculating hazard ratios (HR). Cumulative subsequent TOPs or requests for TOP were analysed by using the Kaplan-Meier method with the log-rank test. The Chi-square test was used as appropriate for categorical variables. To compare distributions between continuous variables, the Mann-Whitney U-test was used. Statistical analyses were performed with IBM SPSS Statistics software, version 24 (IBM Corp., Armonk, NY). Statistical significance was defined as $p<0.05$.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 2305 eligible women undergoing a first trimester TOP at Kätilöopisto hospital, Department of Obstetrics and Gynaecology, Helsinki University Hospital, 1139 were interested in intrauterine contraception, 751 of whom were recruited and randomised between October 18th2010 and January 21st2013. After randomisation, three women decided to continue with the pregnancy, and were excluded from the study. Of all the abortions 141 (18.9%) were surgical and 607 (81.1%) medical.

In the intervention group, 301 (80.3%) women received the IUD within four weeks after the abortion as planned. By three months, 347 (92.5%) women had an IUD inserted. The remaining 28 (7.5%) women did not receive an IUD; 20 (5.3%) women did not attend the follow-up and 8 (2.1%) declined IUD insertion.

In the control group, 76 (20.4%) women received an IUD at the PHC within three months. Additionally, 19 (5.1%) women received an IUD at the hospital within three months, either at the time of surgical abortion or at an additional visit, contrary to the study plan. By one year, a total of 166 (44.5%) women in the control group had an IUD inserted.

The cumulative proportion of women without a subsequent TOP during five years was 89.3% in the intervention and 83.1% in the control group (p=0.010). The cumulative proportions of women without a request for subsequent TOP were 87.7% and 82.3% (p=0.028), respectively (Figure 2). During the 5-year follow-up, 40 (10.7%) women in the intervention and 63 (16.9%) in the control group underwent at least one subsequent induced abortion (HR 1.67 [CI 95% 1.13 to 2.49],

p=0.011) (Table 2). Altogether 16 (2.1%) women (9 in the intervention and 7 in the control group) had more than one subsequent TOP during the 5-year follow-up. The overall numbers of subsequent induced abortions were 50 in the intervention and 72 in the control group, resulting in an incidence of 26.7 *vs*. 38.6/1000 years of follow-up (*p*=0.027).

In the intervention group, 36 (11.8%) of the women undergoing a subsequent TOP had a medical and 4 (5.8%) a surgical index TOP, whereas in the control group the numbers were 49 (16.4%) and 14 (18.9%), respectively. The method of abortion did not explain the risk for subsequent TOP in either group (intervention group: HR 0.46 [CI 95% 0.16 to 1.34], *p*=0.156; control group: HR 1.19 [CI 95% 0.62 to 2.30], *p*= 0.603).

The total number of women requesting termination of a subsequent unwanted pregnancy (including cases of miscarriage, ectopic pregnancy and blighted ovum diagnosed at the time of assessment for TOP) was 46 (12.3%) in the intervention and 66 (17.7%) in the control group (HR 1.52 [CI 95% 1.04 to 2.22], *p*=0.029). There were 58 requests for TOP in the intervention and 76 in the control group (30.9 *vs*. 40.8/1000 years of follow-up, *p*=0.080).

The median time interval between the index TOP and the first subsequent TOP was 792 days (2.17 years [IQR 604–1439 days/1.65–3.94 years]) in the intervention, and 645 days (1.77 years [IQR 337–1076 days/0.92–2.94 years]) in the control group (*p*=0.013).

When looking at subsequent TOPs during the first three years, a significant difference between the groups was seen; the number of women undergoing one or several TOP(s) was 23 (6.1%) in the intervention and 48 (12.9%) in the control group (HR 1.71 [CI 95% 1.04 to 2.81], *p*=0.035). During fourth and fifth year, 17 (4.5%) women in the intervention and 15 (4.0%) in the control group had their first subsequent TOP (HR 1.19 [CI 95% 0.58 to 2.43, *p*=0.631].

The number of women requesting a subsequent TOP during the first three years was 27 (7.2%) in the intervention and 52 (13.9%) in the control group (HR 2.02 [CI 95% 1.27 to 3.22], *p*=0.003), and

during the fourth and fifth year, 19 (5.1%) and 14 (3.8%), respectively (HR 0.80 [CI95% 0.40 to 1.59], *p*=0.523). Altogether 25 TOPs were performed in the intervention group and 52 in the control group (*p*=0.001) during the first three years resulting in an incidence of 22.2 *vs*. 46.5/1000 years of follow-up. However, during the 4th and 5th year there were slightly more TOPs in the intervention (25) than in the control group (20) (33.3 *vs*. 26.8/1000, *p*=0.453). Similarly, the number of all requested TOPs was 30 *vs*. 56 (24.0 *vs*. 46.5/1000, *p*=0.003) during the first three years, and 28 *vs.* 20 (25.3 *vs*. 18.8/1000, *p*=0.240) during the 4th and 5th year.

There were no cases of pregnancy during IUD use. Two women in the intervention group had an unwanted pregnancy due to an unnoticed expulsion of the LNG-IUS; one attended the follow-up visits at three months and one year, when the IUD was found to be *in situ*. The other one reported IUD use at one year but did not attend the 1-year visit.

Based on self-reporting, information collected at the follow-up visits or based on the PHC database of the City of Helsinki, 228 (60.8%) women in the intervention group and 100 (26.8%) women in the control group were known to be currently using IUD at one year. Data on the contraceptive method used at one year were unavailable for 118 (31.5%) women in the intervention and 192 (51.5%) in the control group. Based on these data, the 1-year continuation rate of IUD use in the intervention group was at least 65.7%, but considering the missing data, possibly considerably higher. In the intervention group, 225 (60.0%) women attended the 1-year follow-up, and 202 (89.8%) of them were using IUD at that time. In the control group, the corresponding figures were significantly lower, i.e. 152 (41.4%, *p*<0.001) and 89 (58.6%, *p*<0.001).

The risk for subsequent TOP could not be predicted by smoking (HR 1.29 [0.85 to 1.96], *p*=0.225), parity (1.16 [0.77 to 1.74], *p*=0.488), or history of TOP (0.96 [0.64 to 1.42], *p*=0.827).

Discussion

We find that provision of intrauterine contraception as part of abortion service was effective in reducing both the number of women requesting subsequent TOP as well as the overall number of TOPs. The efficacy of IUD in reducing the need of abortion was limited to the first three years after the index TOP.

The overall rate of subsequent TOP was 14%, which is in line with previous studies as well as the estimates on which the power calculations of the study were based. The total number of subsequent TOPs was reduced by approximately one third during the 5-year follow-up due to the intervention. This is slightly less than the presumed 50% reduction used in the power calculations. However, these figures were derived from studies comparing IUD *vs.* non-IUD contraception (Heikinheimo *et al*., 2008). We found no predictive background factors for the risk of subsequent TOP. Thus, the difference in the rate of subsequent abortion between the two study groups is most likely due to their different rate of IUD use. For example, 93% of the intervention but only 26% of the control group had received the IUD by three months after the abortion (Pohjoranta *et al.*, 2018). The reasons for this are likely to involve factors related both to the individuals as well as to the service provision system separating abortion care from pre- and post-abortion contraceptive care (Duodecim, 2013). Nevertheless, it is noteworthy that even among women who are highly motivated for intrauterine contraception, providing the service as part of abortion care makes a significant difference in IUD uptake and the need for future abortion.

The randomised study setting with a relatively large sample is a strength. The data on subsequent TOPs was obtained from the national abortion register, which is of exceptionally high quality and coverage. In 2011, the coverage of the register was 97% (Heino *et al*., 2018). In our study data, only one recurrent TOP identified in the hospital database was missing from the register data.

Both medical and surgical abortions, with different time points of IUD provision, were included. This may be considered a weakness. However, use of both methods of abortion also reflects the contemporary practice of TOP. Moreover, significant reduction in the need of subsequent TOP was seen following both medical and surgical – and thus different means of IUD provision – index abortion. In addition, due to poor attendance at follow-up and low response rates to the questionnaires, especially in the control group, reliable information about IUD usage during the 5-year follow-up was unavailable.

The study participants were residents of the City of Helsinki, which may limit the generalizability of the results. Also, the study population represents women often in an evolving phase of life, and during the follow-up some of the participants have moved inside Finland or even abroad. Thus, we were unable to receive comprehensive information concerning the contraceptive methods used during the follow-up. However, the data derived from the national abortion register cover all TOPs performed in Finland. Unfortunately, we had no possibility to obtain data on possible subsequent TOPs performed abroad.

It is noteworthy that the effect of intervention was significant during the first 3 years after the index TOP. However, both the number of women requesting subsequent TOP and the overall number of TOPs were approximately similar in both groups during the 4^{th} and 5^{th} year after the index abortion. This is likely explained by discontinuation of IUD use before the follow-up was complete.

The average age at first delivery in Finland is 29.2 years, whereas the median age of the study participants at baseline was 27 years (THL, 2017). Thus, it is likely that many of the participants had planned pregnancies during the five-year follow-up period. Our previous study also supports this; the mean time from abortion to next pregnancy resulting in delivery was three years (Heikinheimo *et al*., 2009). Thus, the effect of the intervention in reducing requested TOPs

dissolved three years after the index abortion. The cost-effectiveness of this intervention is yet to be shown, however in large populations, the provision of IUD post abortion has shown to be cost effective in lowering the number of induced abortions (Ames *et al*., 2012).

A key finding of the study is that the higher incidence of subsequent TOP in the control group was associated with lower uptake of IUD. Besides the randomisation group, few risk factors for not having the IUD inserted could be identified in our previous analysis (Pohjoranta *et al*. 2018). Thus, in abortion care, in order to optimize the high efficacy of IUD in post-abortion contraception, integration of counselling, easy-access service, and early and effective IUD provision is important.

Data sharing

• Deidentified participant data, study protocol, statistical analysis plan and study protocol will be made available.

• These data will be available 6–36 months after publication for investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose.

• Proposals should be directed to oskari.heikinheimo@helsinki.fi.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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Declaration of interest

OH has served on advisory boards for Bayer Healthcare AG, Gedeon-Richter, Sandoz AG, HRA-Pharma and Vifor Pharma, and designed and lectured at educational events of these companies. SS has served as an advisor for Exeltis, Sandoz AG and Gedeon Richter and lectured at educational events of Bayer Healthcare AG. The other authors have no conflicts of interests to declare.

Contributors

All authors have contributed to planning the study protocol. EP, SS, PI, MM and OH were responsible for the clinical visits. MG has provided the data from the national health registers. PI has recruited and interviewed the participants and arranged the appointments. EP has performed the statistical analysis and written the first draft of the report with input from SS and OH. SS and OH were responsible for the overall study and obtained funding.

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477 **Figure legends:**

478

479 Figure 1. Study flow chart.

480 Figure 2. Cumulative proportions of women without subsequent TOP or requested TOP during

481 five-year follow-up.

482 Figure 3A. Annual rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).

483 Figure 3B. Average rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).

Early provision of intrauterine contraception as part of abortion care – 5-year results of a randomised controlled trial

Running title: Early provision of IUD as part of abortion care

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Abstract

Study question: Can the incidence of subsequent termination of pregnancy (TOP) be diminished by providing intrauterine contraception as part of abortion services?

Summary answer: Provision of IUD as part of TOP services reduced the need for subsequent TOP during 5-year follow-up, but the effect was limited to the first three years.

What is known already: IUD is highly effective in preventing subsequent TOP. Prompt initiation of IUD leads to higher usage rate during follow-up, as compliance with post-TOP IUD insertion visits is low.

Study design, size, duration: The objective of this randomised controlled trial was to assess the effect of early comprehensive provision of intrauterine contraception after TOP on the incidence of subsequent TOP during five years of follow-up.

This study was conducted at Helsinki University Hospital between October 18th 2010 and January 21st 2013. Altogether 748 women undergoing a first trimester TOP were recruited and randomised into two groups. The intervention group (n=375) was provided with an IUD during surgical TOP or 1–4 weeks following medical TOP at the hospital providing the abortion care. Women in the control group (n=373) were advised to contact primary health care for follow-up and IUD insertion. Subsequent TOPs during the 5-year follow-up were identified from the Finnish Register on induced abortions.

Participants, setting, methods: The inclusion criteria were age ≥ 18 years, duration of gestation ≤12 weeks, residence in Helsinki and accepting intrauterine contraception. Women with contraindications to IUD were excluded.

Main results and the role of chance: The overall numbers of subsequent TOPs were 50 in the intervention and 72 in the control group (26.7 vs. 38.6/1000 years of follow-up, p=0.027) and

those of requested TOPs including TOPS and early pregnancy failures 58 and 76 (30.9 vs. 40.8/1000, p=0.080). Altogether 40 (10.7%) women in the intervention and 63 (16.9%) in the control group underwent one or several subsequent TOPs (HR 1.67 [CI 95% 1.13 to 2.49], p=0.011). The number of TOPs was reduced by the intervention during years 0–3 (22.2 vs. 46.5/1000, p=0.035), but not during years 4–5 (33.3 vs. 26.8/1000, p=0.631).

Limitations, reasons for caution: Both medical and surgical TOP were used. This may be seen as a limitation, but it also reflects the contemporary praxis of abortion care. The immediate post-TOP care were provided by two different organizations allowing us to compare two different ways of contraceptive service provision following TOP.

Wider implications of the findings: Providing TOP and IUD insertion comprehensively in a same heath care unit leads to significantly higher rates of attendance, IUD use and significantly lower risk of subsequent TOP (HR 1.67 [CI 95% 1.13 to 2.49], *p*=0.011).

Study funding/competing interest(s): This study was supported by Helsinki University Central Hospital Research funds and by research grants provided by the Jenny and Antti Wihuri Foundation, the Yrjö Jahnsson Foundation, and Finska Läkaresällskapet. EP has received a personal research grant from the Finnish Medical Society. The City of Helsinki supported the study by providing the IUDs. The funding organisations had no role in planning or execution of the study, or in analysing the study results.

Trial registration number: The trial was registered at clinicaltrials.gov (NCT01223521).

Trial registration date: 18th October 2010.

Date of first patient's enrolment: 18th October 2010.

Keywords: Abortion/termination of pregnancy, IUD/intrauterine contraception, subsequent TOP

Ethics approval

We received approvals from the Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS 260/13/03/03/2009), the Ethics Committee of the City of Helsinki (10-1138/054). Approval to carry out the study was granted by the Hospital District of Helsinki and Uusimaa (§12/30.03.2010). The Finnish Institute for Health and Welfare (THL) granted an approval to use personal-level data, which is required for registry-based studies in Finland (THL/1479/5.05.00/2013). All personal-level data that could be used to identify individuals was removed before the analyses.

Transparency statement

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient and public information statement

The study was initiated in 2009, and at the time it was not customary to involve patients and/or public in planning of a scientific study.

Dissemination declaration

The study results will be disseminated to the health care providers and organizations involved in the study as well as to the public once the study has been published.

87

88 ## Introduction

89 The efficacy of long-acting reversible contraceptives (LARCs) and, especially, that of intrauterine
90 devices (IUD) in preventing unwanted pregnancy is well established (Peipert *et al*., 2012; Winner
91 *et al*., 2012; Blumenthal *et al*., 2011; Secura *et al*., 2014). According to several recent guidelines,
92 LARCs have become the recommended method of contraception for women in all age groups
93 (WHO, 2015; RCOG, 2018).
94 Previous cohort studies have shown that young age, parity, and history of termination of
95 pregnancy (TOP) are associated with increased risk of subsequent TOP (Heikinheimo *et al*., 2008).
96 In addition, contraceptive choices affect the risk of subsequent unwanted pregnancy. In cohort
97 studies, post-abortal use of IUD has been associated with a 60–70% reduction in the need of
98 subsequent TOP (Okusanya *et al*., 2014; Rose *et al*., 2012).
99 Regardless of the method of TOP, the resumption of ovarian function occurs rapidly; 80% of
100 women ovulate within 6 weeks after TOP (Schreiber *et al*., 2011). In addition, 50% of women
101 resume sexual activity in two weeks following TOP (Boesen *et al*., 2004). Thus, in order to prevent
102 subsequent unwanted pregnancy, immediate initiation of effective contraception is important. In
103 Finland, contraceptive counselling and planning are routinely included in the TOP process, and
104 women are advised to initiate contraceptive use immediately. Yet, more than one in three women
105 undergoing a TOP have a history of one or several previous TOPs. Similar to several other
106 countries, this rate has been increasing during the past decade in Finland (THL, 2018;
107 Socialstyrelsen, 2018; INED, 2012; GOV.UK, 2018).
108 The insertion of IUD at the time of surgical TOP is effective and safe, and results in higher IUD use
109 during follow-up (Okusanya *et al*., 2014; WHO, 2012; Sääv *et al*., 2012; Bednarek *et al*., 2011).

However, medical abortion has become the dominant method in several countries during the last decades (THL, 2018; Socialstyrelsen, 2018; INED, 2012; GOV.UK, 2018). Medical abortion poses challenges concerning IUD provision since compliance with post-abortion care in the service-delivery systems assessed is often poor (Betstadt *et al*., 2011; Pohjoranta *et al*., 2018). Immediate insertion of an IUD after medical TOP (MTOP) is safe, although it is associated with a higher risk of partial expulsion (Korjamo *et al*., 2017). In contrast, IUD provision at approximately one week after MTOP does not significantly increase the risk of expulsion (Sääv *et al*., 2012; Shimoni *et al*., 2011; Betstadt *et al*., 2011). As with surgical abortion, the prompt provision of IUD leads to a higher rate of use and subject satisfaction following MTOP (Sääv *et al*., 2012).

In the present study, we studied the efficacy of routine provision of IUD as part of abortion care in comparison to the current praxis of prescribing oral contraceptives as a bridging method and directing women to primary health care (PHC) for IUD insertion. Our primary outcome measure was the number of subsequent TOPs performed during the 5-year follow-up after the index abortion. The secondary outcomes were the number of all requested TOPs during the follow-up (including cases of miscarriage, blighted ovum or ectopic pregnancy) and the timing of subsequent TOP. Previously, we published the 1-year follow-up results concerning the need for subsequent TOP, success of early IUD insertion, rates of attendance and IUD use, as well as mental and sexual well-being (Pohjoranta *et al*., 2015; Pohjoranta *et al*., 2017; Pohjoranta *et al*., 2018; Toffol *et al*., 2016). In the present study, we report the final 5-year results on the need for subsequent TOP.

Methods

Study design and participants

This study design has been described in detail previously (Pohjoranta *et al*., 2015). The study was conducted in collaboration with the Helsinki University Hospital and the City of Helsinki.

The inclusion criteria were age ≥18 years, residence in Helsinki, duration of gestation ≤12^{+0} weeks, having a non-foetal indication for the abortion and signing an informed consent form. Women with uterine anomaly, cervical screening result requiring surgical intervention, or inadequate language skills in Finnish or Swedish were excluded. Acute liver disease and breast cancer were contraindications for the levonorgestrel-releasing intrauterine system (LNG-IUS), and copper allergy, iron deficiency anaemia, and Wilson's disease for copper intrauterine device (Cu-IUD). The characteristics of the study participants are presented in Table 1.

Altogether 751 women were randomised into two groups (Figure 1). Women in the intervention group (n=375) were provided with an IUD (either the 52mg levonorgestrel-releasing intrauterine system, LNG-IUS, Mirena® or a Cu-IUD, Nova-T®, both manufactured by Bayer Ag [Turku, Finland] and hereafter referred as IUD) at the hospital responsible for the abortion care. The IUD was planned to be inserted at the time of surgical abortion (n=70), or at a follow-up visit performed 1–4 weeks after MTOP (n=305). Women in the control group (n=373 [71 cases of surgical and 302 medical abortion]) were prescribed oral contraceptives and advised to contact their PHC unit for follow-up and contraceptive services including IUD insertion, according to the current national guideline on induced abortion (Duodecim, 2013). The subsequent TOPs were analysed on an intention-to-treat analysis (ITT) to assess the efficacy of the intended intervention.

Procedures

All abortions were performed according to the national guideline (Duodecim, 2013). All the index abortions in this study were performed due to a social indication, or based on the woman's age of at least 40 years or having given birth to four or more children, both indications for abortion given in the Finnish legislation. The participants were advised to contact the hospital in case of suspected abortion-related adverse events or complications.

According to local guideline of the time, all women were invited for a follow-up at three months after IUD insertion. For the intervention group, this was performed by study nurse. All women were provided a follow-up visit by a specialist in obstetrics and gynaecology (SS) at one and five years at the PHC family planning clinic of the City of Helsinki.

Data on subsequent induced abortions during five years after the index abortion were obtained from the Finnish Register of Induced Abortions kept by the Finnish Institute for Health and Welfare (THL). In Finland, reporting all TOPs to THL is mandatory by the law, and thus the coverage of the register is very high (Heino *et al*., 2018). These data were complemented with data from the electronic patient files of the Hospital District of Helsinki and Uusimaa, where also the requested TOPs later diagnosed as ectopic pregnancies or miscarriages were identified. All cases were reviewed by two members of the study team. In case of a disagreement, a third review was performed. IUD insertion and usage in the control group was followed up to one year using the electronic patient files of the PHC of the City of Helsinki.

Outcomes

The primary outcome of the study was the number of subsequent TOP during five years of follow-up. As a secondary outcome, we analysed all requested TOPs, including cases of miscarriage, ectopic pregnancy or blighted ovum, diagnosed at the time of assessment for TOP.

Randomisation and masking

Randomisation was performed by using computer-assisted permuted-block method with random block sizes of four to six. The investigators did not participate in randomisation, which was done before commencing the study. The group assignments were kept in sealed envelopes, which the study nurse opened after informing and recruiting the women.

Statistical analysis

Based on previous studies, a 15% incidence for subsequent abortion during five years was assumed (Heikinheimo *et al*., 2008). The power calculation was performed with an assumption that the intervention would cause a 50% decrease in the incidence of subsequent abortion. By using the log-rank test, for a power of 80% and a 5% significance level, a total of 350 participants were needed for each group. To cover for the possible loss-to follow-up, 751 women were randomised, and finally 748 women were included in the study. (Figure 1)

The outcomes were calculated by one thousand follow-up years. The Cox proportional hazards model was used for calculating hazard ratios (HR). Cumulative subsequent TOPs or requests for TOP were analysed by using the Kaplan-Meier method with the log-rank test. The Chi-square test was used as appropriate for categorical variables. To compare distributions between continuous variables, the Mann-Whitney U-test was used. Statistical analyses were performed with IBM SPSS Statistics software, version 24 (IBM Corp., Armonk, NY). Statistical significance was defined as $p<0.05$.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 2305 eligible women undergoing a first trimester TOP at Kätilöopisto hospital, Department of Obstetrics and Gynaecology, Helsinki University Hospital, 1139 were interested in intrauterine contraception, 751 of whom were recruited and randomised between October 18th2010 and January 21st2013. After randomisation, three women decided to continue with the pregnancy, and were excluded from the study. Of all the abortions 141 (18.9%) were surgical and 607 (81.1%) medical.

In the intervention group, 301 (80.3%) women received the IUD within four weeks after the abortion as planned. By three months, 347 (92.5%) women had an IUD inserted. The remaining 28 (7.5%) women did not receive an IUD; 20 (5.3%) women did not attend the follow-up and 8 (2.1%) declined IUD insertion.

In the control group, 76 (20.4%) women received an IUD at the PHC within three months. Additionally, 19 (5.1%) women received an IUD at the hospital within three months, either at the time of surgical abortion or at an additional visit, contrary to the study plan. By one year, a total of 166 (44.5%) women in the control group had an IUD inserted.

The cumulative proportion of women without a subsequent TOP during five years was 89.3% in the intervention and 83.1% in the control group (p=0.010). The cumulative proportions of women without a request for subsequent TOP were 87.7% and 82.3% (p=0.028), respectively (Figure 2). During the 5-year follow-up, 40 (10.7%) women in the intervention and 63 (16.9%) in the control group underwent at least one subsequent induced abortion (HR 1.67 [CI 95% 1.13 to 2.49],

p=0.011) (Table 2). Altogether 16 (2.1%) women (9 in the intervention and 7 in the control group) had more than one subsequent TOP during the 5-year follow-up. The overall numbers of subsequent induced abortions were 50 in the intervention and 72 in the control group, resulting in an incidence of 26.7 *vs*. 38.6/1000 years of follow-up (*p*=0.027).

In the intervention group, 36 (11.8%) of the women undergoing a subsequent TOP had a medical and 4 (5.8%) a surgical index TOP, whereas in the control group the numbers were 49 (16.4%) and 14 (18.9%), respectively. The method of abortion did not explain the risk for subsequent TOP in either group (intervention group: HR 0.46 [CI 95% 0.16 to 1.34], *p*=0.156; control group: HR 1.19 [CI 95% 0.62 to 2.30], *p*= 0.603).

The total number of women requesting termination of a subsequent unwanted pregnancy (including cases of miscarriage, ectopic pregnancy and blighted ovum diagnosed at the time of assessment for TOP) was 46 (12.3%) in the intervention and 66 (17.7%) in the control group (HR 1.52 [CI 95% 1.04 to 2.22], *p*=0.029). There were 58 requests for TOP in the intervention and 76 in the control group (30.9 *vs*. 40.8/1000 years of follow-up, *p*=0.080).

The median time interval between the index TOP and the first subsequent TOP was 792 days (2.17 years [IQR 604–1439 days/1.65–3.94 years]) in the intervention, and 645 days (1.77 years [IQR 337–1076 days/0.92–2.94 years]) in the control group (*p*=0.013).

When looking at subsequent TOPs during the first three years, a significant difference between the groups was seen; the number of women undergoing one or several TOP(s) was 23 (6.1%) in the intervention and 48 (12.9%) in the control group (HR 1.71 [CI 95% 1.04 to 2.81], *p*=0.035). During fourth and fifth year, 17 (4.5%) women in the intervention and 15 (4.0%) in the control group had their first subsequent TOP (HR 1.19 [CI 95% 0.58 to 2.43, *p*=0.631].

The number of women requesting a subsequent TOP during the first three years was 27 (7.2%) in the intervention and 52 (13.9%) in the control group (HR 2.02 [CI 95% 1.27 to 3.22], *p*=0.003), and

during the fourth and fifth year, 19 (5.1%) and 14 (3.8%), respectively (HR 0.80 [CI95% 0.40 to 1.59], *p*=0.523). Altogether 25 TOPs were performed in the intervention group and 52 in the control group (*p*=0.001) during the first three years resulting in an incidence of 22.2 *vs*. 46.5/1000 years of follow-up. However, during the 4th and 5th year there were slightly more TOPs in the intervention (25) than in the control group (20) (33.3 *vs*. 26.8/1000, *p*=0.453). Similarly, the number of all requested TOPs was 30 *vs*. 56 (24.0 *vs*. 46.5/1000, *p*=0.003) during the first three years, and 28 *vs.* 20 (25.3 *vs*. 18.8/1000, *p*=0.240) during the 4th and 5th year.

There were no cases of pregnancy during IUD use. Two women in the intervention group had an unwanted pregnancy due to an unnoticed expulsion of the LNG-IUS; one attended the follow-up visits at three months and one year, when the IUD was found to be *in situ*. The other one reported IUD use at one year but did not attend the 1-year visit.

Based on self-reporting, information collected at the follow-up visits or based on the PHC database of the City of Helsinki, 228 (60.8%) women in the intervention group and 100 (26.8%) women in the control group were known to be currently using IUD at one year. Data on the contraceptive method used at one year were unavailable for 118 (31.5%) women in the intervention and 192 (51.5%) in the control group. Based on these data, the 1-year continuation rate of IUD use in the intervention group was at least 65.7%, but considering the missing data, possibly considerably higher. In the intervention group, 225 (60.0%) women attended the 1-year follow-up, and 202 (89.8%) of them were using IUD at that time. In the control group, the corresponding figures were significantly lower, i.e. 152 (41.4%, *p*<0.001) and 89 (58.6%, *p*<0.001).

The risk for subsequent TOP could not be predicted by smoking (HR 1.29 [0.85 to 1.96], *p*=0.225), parity (1.16 [0.77 to 1.74], *p*=0.488), or history of TOP (0.96 [0.64 to 1.42], *p*=0.827).

Discussion

We find that provision of intrauterine contraception as part of abortion service was effective in reducing both the number of women requesting subsequent TOP as well as the overall number of TOPs. The efficacy of IUD in reducing the need of abortion was limited to the first three years after the index TOP.

The overall rate of subsequent TOP was 14%, which is in line with previous studies as well as the estimates on which the power calculations of the study were based. The total number of subsequent TOPs was reduced by approximately one third during the 5-year follow-up due to the intervention. This is slightly less than the presumed 50% reduction used in the power calculations. However, these figures were derived from studies comparing IUD *vs.* non-IUD contraception (Heikinheimo *et al*., 2008). We found no predictive background factors for the risk of subsequent TOP. Thus, the difference in the rate of subsequent abortion between the two study groups is most likely due to their different rate of IUD use. For example, 93% of the intervention but only 26% of the control group had received the IUD by three months after the abortion (Pohjoranta *et al.*, 2018). The reasons for this are likely to involve factors related both to the individuals as well as to the service provision system separating abortion care from pre- and post-abortion contraceptive care (Duodecim, 2013). Nevertheless, it is noteworthy that even among women who are highly motivated for intrauterine contraception, providing the service as part of abortion care makes a significant difference in IUD uptake and the need for future abortion.

The randomised study setting with a relatively large sample is a strength. The data on subsequent TOPs was obtained from the national abortion register, which is of exceptionally high quality and coverage. In 2011, the coverage of the register was 97% (Heino *et al*., 2018). In our study data, only one recurrent TOP identified in the hospital database was missing from the register data.

Both medical and surgical abortions, with different time points of IUD provision, were included. This may be considered a weakness. However, use of both methods of abortion also reflects the contemporary practice of TOP. Moreover, significant reduction in the need of subsequent TOP was seen following both medical and surgical – and thus different means of IUD provision – index abortion. In addition, due to poor attendance at follow-up and low response rates to the questionnaires, especially in the control group, reliable information about IUD usage during the 5-year follow-up was unavailable.

The study participants were residents of the City of Helsinki, which may limit the generalizability of the results. Also, the study population represents women often in an evolving phase of life, and during the follow-up some of the participants have moved inside Finland or even abroad. Thus, we were unable to receive comprehensive information concerning the contraceptive methods used during the follow-up. However, the data derived from the national abortion register cover all TOPs performed in Finland. Unfortunately, we had no possibility to obtain data on possible subsequent TOPs performed abroad.

It is noteworthy that the effect of intervention was significant during the first 3 years after the index TOP. However, both the number of women requesting subsequent TOP and the overall number of TOPs were approximately similar in both groups during the 4^{th} and 5^{th} year after the index abortion. This is likely explained by discontinuation of IUD use before the follow-up was complete.

The average age at first delivery in Finland is 29.2 years, whereas the median age of the study participants at baseline was 27 years (THL, 2017). Thus, it is likely that many of the participants had planned pregnancies during the five-year follow-up period. Our previous study also supports this; the mean time from abortion to next pregnancy resulting in delivery was three years (Heikinheimo *et al*., 2009). Thus, the effect of the intervention in reducing requested TOPs

dissolved three years after the index abortion. The cost-effectiveness of this intervention is yet to be shown, however in large populations, the provision of IUD post abortion has shown to be cost effective in lowering the number of induced abortions (Ames *et al*., 2012).

A key finding of the study is that the higher incidence of subsequent TOP in the control group was associated with lower uptake of IUD. Besides the randomisation group, few risk factors for not having the IUD inserted could be identified in our previous analysis (Pohjoranta *et al*. 2018). Thus, in abortion care, in order to optimize the high efficacy of IUD in post-abortion contraception, integration of counselling, easy-access service, and early and effective IUD provision is important.

Data sharing

• Deidentified participant data, study protocol, statistical analysis plan and study protocol will be made available.

• These data will be available 6–36 months after publication for investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose.

• Proposals should be directed to oskari.heikinheimo@helsinki.fi.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

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Declaration of interest

OH has served on advisory boards for Bayer Healthcare AG, Gedeon-Richter, Sandoz AG, HRA-Pharma and Vifor Pharma, and designed and lectured at educational events of these companies. SS has served as an advisor for Exeltis, Sandoz AG and Gedeon Richter and lectured at educational events of Bayer Healthcare AG. The other authors have no conflicts of interests to declare.

Contributors

All authors have contributed to planning the study protocol. EP, SS, PI, MM and OH were responsible for the clinical visits. MG has provided the data from the national health registers. PI has recruited and interviewed the participants and arranged the appointments. EP has performed the statistical analysis and written the first draft of the report with input from SS and OH. SS and OH were responsible for the overall study and obtained funding.

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477 **Figure legends:**

478

479 Figure 1. Study flow chart.

480 Figure 2. Cumulative proportions of women without subsequent TOP or requested TOP during

481 five-year follow-up.

482 Figure 3A. Annual rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).

483 Figure 3B. Average rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).

Table 1. Baseline characteristics of the study participants. The data are presented as n (%) unless stated otherwise.

	Intervention group (n=375)	**Control group (n=373)**	**p-value**
Age (years); median (IQR)	27 (11)	27 (10)	0.489
Marital status			0.157
Single	202 (53.9)	229 (61.4)	
Cohabiting	102 (27.2)	92 (24.7)	
Married	71 (18.9)	52 (13.9)	
Regular smoking	188 (50.1)	189 (51.4)	0.710
Regular use of alcohol	275 (73.3)	286 (77.9)	0.145
Contraceptive method used prior to index TOP			0.335
Combined hormonal contraception*	45 (12.0)	49 (13.1)	
Progestin-only pill	12 (3.2)	9 (2.4)	
Cu-IUD	–	1 (0.3)	
Condom	159 (42.4)	135 (36.2)	
Other	8 (2.1)	14 (3.8)	
None	151 (40.3)	165 (44.2)	
History of delivery	187 (49.9)	175 (46.9)	0.501
History of TOP	174 (46.4)	153 (41.0)	0.095
Method of abortion			
Surgical	69 (18.4)	74 (19.8)	0.617
Medical	306 (81.6)	299 (80.2)	
Duration of index pregnancy (days); median (IQR)	57 (17)	56 (16)	0.208

* Combined oral contraceptive pill, patch or ring

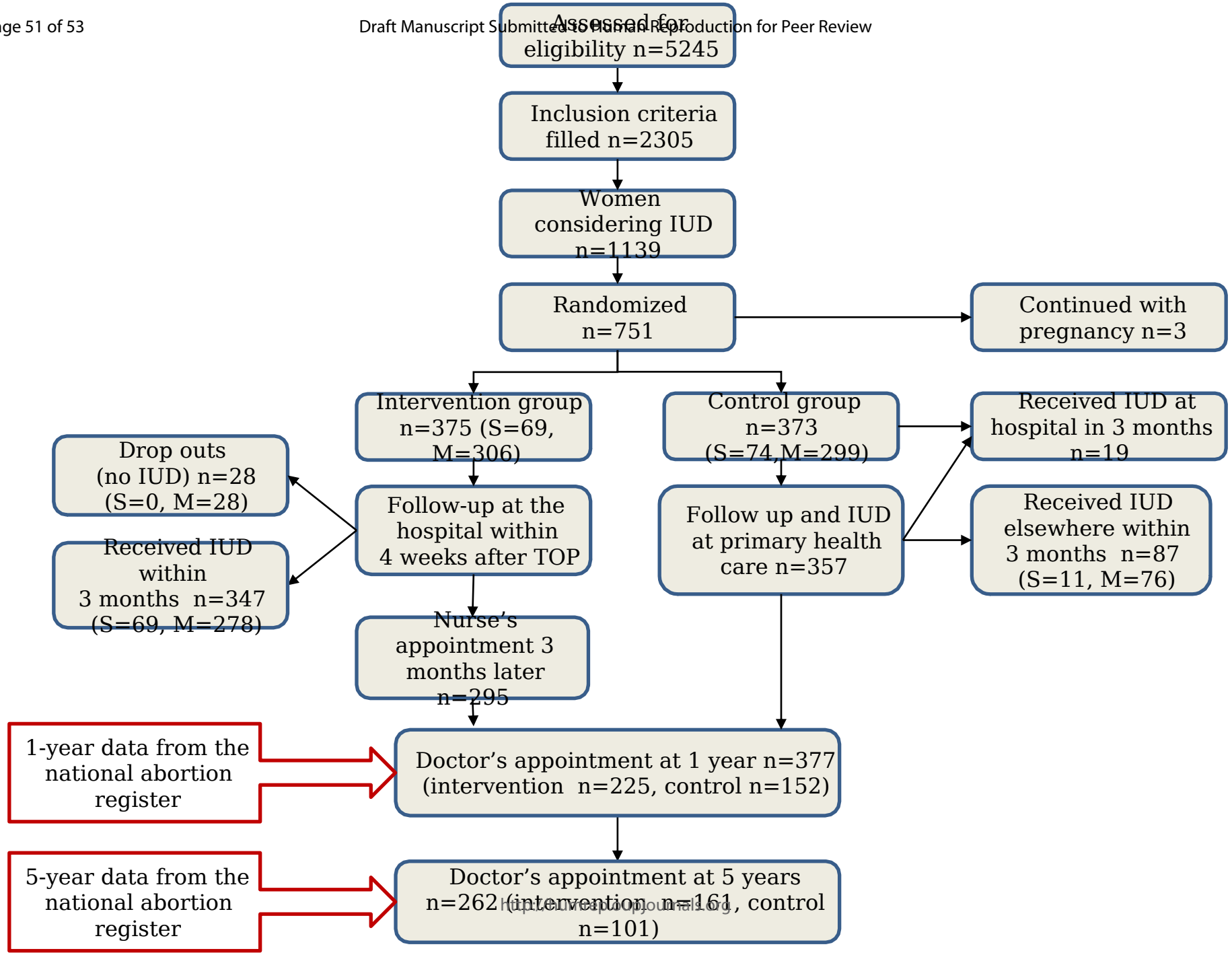
Table 2. Subsequent TOP(s) and requested TOP(s) during five-year follow-up.

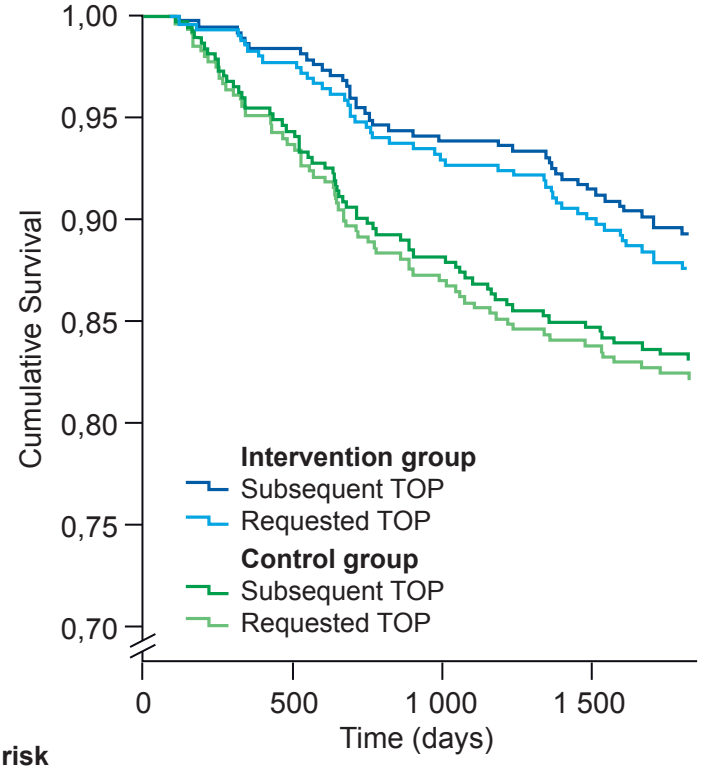
	Intervention group n=375 (%)	**Control group n=373 (%)**	**HR (CI 95%)**	***p*-value**
Women with subsequent TOP(s)	40 (10.7)	63 (16.9)	1.67 (1.13–2.49)	0.011*
Women with requested TOP(s)	46 (12.3)	66 (17.7)	1.52 (1.04–2.22)	0.029*
Subsequent TOP - **Number** - **Incidence*** **	 50 26.7	 72 38.6	 –	 0.027**
Requests for TOP - **Number** - **Incidence*** **	 58 30.9	 76 40.8	 –	 0.080**

* Log rank test

** Chi square test

*** Number of TOP/1000 years of follow-up





Number at risk

Intervention group				
Subsequent TOP	375	369	352	343
Requested TOP	375	367	349	338
Control group				
Subsequent TOP	373	352	329	316
Requested TOP	373	350	325	313

Subsequent TOP: HR 1.67 (CI 95% 1.13–2.49); p=0.011.
Requested TOP: HR 1.52 (CI 95% 1.04–2.22); p=0.029.

Figure 3A. Rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).

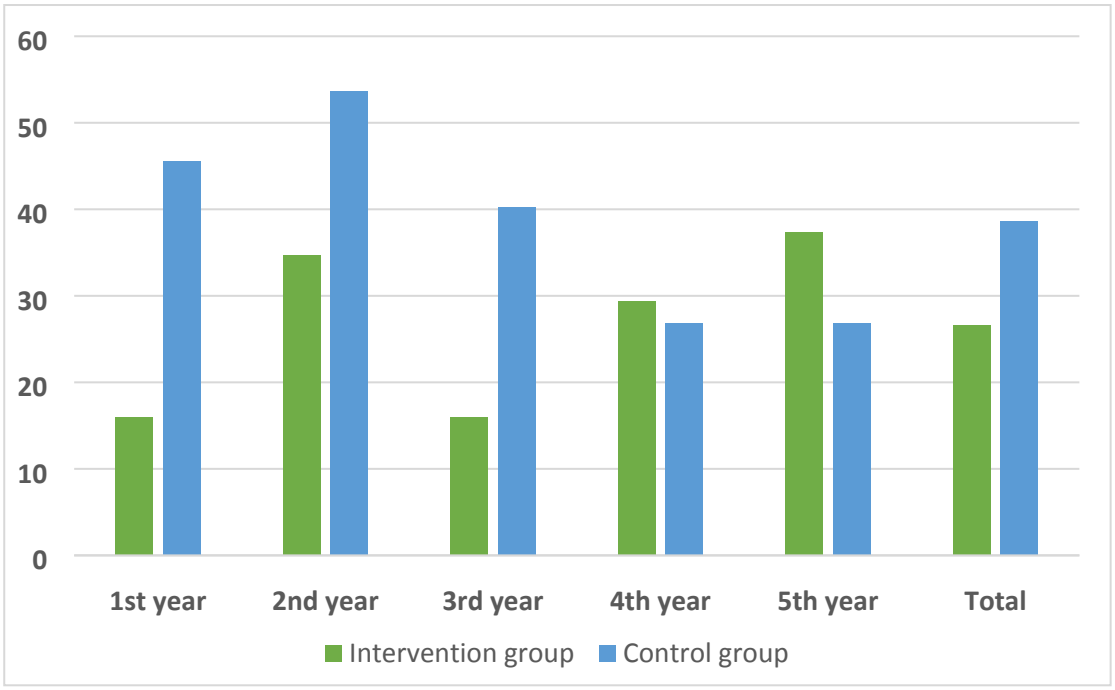


Figure 3B. Average rate of subsequent TOP during five-year follow-up (/1000 years of follow-up).